CONTROLLED AND CONTINUED DELIVERY OF RIFAXIMIN AND/OR OTHER SUBSTANCES

Description

The progress of the dental technique and the medical treatment of these last years has carried to excellent solutions for nearly the totality of dental pathologies regarding hard tissues such as tooth and bone, but not for periodontal tissue and gum, that also carry out an extremely important role in the conservation and good functionality of the masticator apparatus.

The periodontal tissue and the gum in particular assures to the system tooth-periodontal tissue-bone an essential protection from all those pathogenic and destabilizing agents that come from the oral cavity.

Moreover chronic infections in the oral cavity are absolute insensitive to systemic treatment by means of antibiotic. One of the scopes of present the invention is to supply adequate means for the protection of the masticator apparatus and drug delivery in the oral cavity, using material adapted for this purpose.

rifaximin is known like a powerful and effective antibiotic to wide number of pathogenic agents. Its use is currently relegated to the treatment of the diarrheas and internal infections. One characteristic that renders precious such an antibiotic is that it does not permeate through the mucosae. This fact allows a local use of such an antibiotic at high concentrations, with a great efficacy, a null systemic concentration and therefore collateral effects. On the other hand, the rifaximin possesses a very low solubility in the physiological liquids. For this reasons it remains in form of small crystal, of intense red color, dispersed in the place of somministration. For aesthetic reasons, this fact prevents its use in all those places, like the mouth, where the patient wishes to maintain a socially acceptable aspect. Moreover, the drug in the form of small crystals, generates a peaky of concentration, at the moment of the application but then it disperses itself quickly far away from the point where it is placed losing its effectiveness. In truth, a continuous and calibrated delivery along the time of rifaximin would be a very good tool for the treatment of a wide ensemble of gram-positive and gram-negative bacteria and it renders possible its use outside of the intestine.

An important class of materials is that one of the, so-called, bi-phasic materials. They are constituted from two phases: a solid one, made by an elastic matrix that maintains its own shape and is able to confer to the material a strong rubber-like elasticity, and a liquid part that fills up its pores that, in gels, are constituted by the molecular interstices. Their importance is given by the fact that the overwhelming majority of biological tissues, for instance, the cartilage, the derma, the endothelia, the tendons, the gray matter of the brain, the chromosomes and the several organelles of the cell are made up of bi-phasic materials. They can have a strong elasticity and can be resistant to repeated cycles of loading like tendons. The volume and the shape that a bi-phasic materials assume derive from the equilibrium of many forces; in exemplified way, it can be said that the fluid enters in the pores, or in the inter-molecular spaces of the solid matrix (polymer network), and swells it for an effect of "suction". This phenomenon is generated from the affinity (attractive force) existing between the molecules of the fluid and those of the solid matrix. The solid matrix (polymer networks) opposes itself to this swelling tendency till an equilibrium volume is reached.

Varying the affinity between the polymer network, constituting the solid matrix, and the fluid, the water content inside of a biphasic material can be regulated. Usually the ratio in weight between fluid (water) and solid part (polymer net) can arrive to advanced values also to 10. The present invention consists in having designed a new method and way of somministrazione of the rifaximin dosed and continued in the time, by means of the formulation and realization of suited bi-phasic materials and devices that allow it.

By means of the devices, matter of this patent, the use of the rifaximin becomes possible outside the intestine (e.g., in the oral and pharyngeal or nasal cavity, in the rectum and vagina). In particular they allows high level, constant in time, of concentration of rifaximin in aqueous body fluids avoiding the intense red color that it produces in the neighboring of the place of somministration.

The claims at the bottom of the present description define the invention.

In particular, the invention sees the employment of a solid and elastic matrix that contains an interstitial fluid. The material contains, together with the interstitial liquid, the medicinal one in crystals, that melting themselves into the interstitial liquid, gradually let antibiotic to diffuse outside. The material systems have been conceived, and this is one of

the aspects of this invention, with the property to enhance the dissolution of rifaximin in the interstitial solution to a very high level.

Moreover, objects of the present invention consist also in the use of the mechanism of the fluid absorption (water) inside the biphasic materials, with the intent to regulate the delivery of the rifaximin.

Here, we make an example of a material synthesis even if, all poly-acid, poly-basic and poly-amphoteric polymers (for instance equipped of carboxylic and/or aminic groups) or hydrophilic ones like: poly-saccharides (xanthan, guar and similar), cellulose-derivatives, alkyl-cellulose, hydroxy-alchyl-cellulose, polyvinyl-sulfonates, poly-acrylates, polyacrylammides and similar ones, polycarboxylates of vinyl and hydroxypropylmethyl-cellulose are equally useful for obtaining a bi-phasic material for controlled and continued delivery of rifaximin.

Example: hydrogel described in EP-A-0 058 497, as an example but not exclusively, poly-vinyl- alcohol (PVA) (of molecular weight preferably but not exclusively between 500.000 and 10.000) dissolved in water, preferably but not exclusively to a concentration of 10% in weight.

In this solution - but a procedure is also possible that does not preview it – it is added the poly-acrylic acid (preferably but not exclusively of a molecular weight between 4.000.000 and 500) up to a concentration, preferably but not exclusively, between 0,2% and 20% in weight. All those poly-acrylic polymers, as those ones commercially available under the trademark Carbopol and Carbomer must be considered equivalents to the poly-acrylic acid.

In this solution jaluronic-acid - but a procedure is possible also that it does not preview it – (preferably but not exclusively of molecular weight between 4.000.000 and 100, and in a concentration between 0,5% and 20% in weight) can be added.

In this solution a bio- adhesive polymer (later on indicated more simply like adhesive) may be dissolved (but a procedure is possible also that it does not preview it), preferably but not exclusively: silicones polymers, poly-isobutylene, acrylic polymers, poly-oxyethylene, Polycarbophil, Carbopol, hydroxy-propyl-methyl-cellulose, carboxy-methyl-cellulose, hydroxy-propyl-cellulose, hydroxy-ethyl-cellulose, Guar rubber, alginates; drum-dried waxy maize starch (more commonly indicated with acronym DDWM).

In this solution the rifaximin in dissolved up to a concentration, preferably but not exclusively, between 0,5% and 30% by weight.

In order to make such a solution of the desired consistency and porosity, it is submitted to cycles of freezing and warming up (preferably but not exclusively in number between one and nine, preferably but not exclusively in an interval of temperature between-90°C and +20°C).

In alternative, in order to make such a solution of the desired solid consistency and porosity, it can be submitted to drying process (preferably but not exclusively at a temperature between 35 °C and 40°C) or to the freezing-drying procedure like described by C. Callens, And Adrians, K.Dierckens, J.P. Remon on journal of the Controlled Release, volume 76 of year (2001), to page 83.

Equivalently, in order to make such a solution of the desired solid consistency and porosity, a divalent salt (preferably but not exclusively, calcium chloride) up to a concentration (preferably but not exclusively) of 2% by weight, can be dissolved in it.

Optionally, in association with the rifaximin, the solid-gel material can contain and delivery others drugs such as antibiotics and/or an anti-inflammatory and/or a pain-relief and/or anesthetic ones that could be useful for a better effect.

In the following it can be found a description that shows a practical, preferable but not exclusive, realization of the device for the delivery of rifaximin in the oral cavity.

In the Fig. 1 it is shown the device in shape of film,

The Fig. 2 shows the section of the device following the line - of figure 1, when adhesive, put in 2, it is stirred homogenously inside the polymer material 1;

Fig. 3 shows the section of the device following the line - of figure 1, when the adhesive film, with or without holes, 3, it is applied to the external surface of the material containing the drug;

Fig. 4 shows the section of the device following the line - of figure 1, when a bi-adhesive film, with or without holes, 4, it is applied to the internal surface of the polymer material.

The way of application of the device, described in this invention, can happen by means of a simple pressure, in the place of interest, in order to let the adhesive attach to the gum or toot and to guarantee the effectiveness of the drug delivery.

The device can be placed directly in contact with the mucosa or other tissue of the oral cavity, and the adhesive element 3 (with or without holes) overlapping the material and going beyond the same, joins the surface of the neighboring gum (or other tissue) to guarantee its stability.

In an alternative way, the device can be placed directly in contact with the mucosa or other tissue of the oral cavity, with the bi-adhesive element, 4, between the mucosa, and the device itself.

Moreover, the rubber-like gel material can be tailored to the wanted shape and placed in a periodontal pocket between the periodontal tissue and the gum for the release of the rifaximin and, eventually, others antibiotics effective for the bacterial flora present in that place.

The rubber-like gel material can be also attached onto the surface of a catheter by dipping or coatings or by others conventional means to delivery rifaximin.

A further application of the device is its use in the rectum or in the vagina. This can be obtained by means of the same material, preferably but not exclusively, in cylindrical shape with a rounded off extremity (like a candle), with eventually, the mean for its extraction and recovery at the end of its use.

CLAIMS

1. A material, preferably but not exclusively bi-phasic constituted by a solid matrix with pores or molecular interstices filled by a fluid, to protect the gum and/or tooth and/or periodontal tissues from the traumatizing collision of the food during the mastication.
2. A material, as defined by claim 1, that also allows the controlled and continued delivery of drugs and/or others substances.
3. A material, as defined by claim 2, for controlled and continued delivery of drugs and/or others substances in the pharyngeal and/or nasal cavity.
4. A material, as defined by the claims 1-3, allowing controlled and continued delivery of antibiotics.
5. A material, as defined by claim 4, allowing controlled and continued delivery of rifamycin.
6. A material as defined by the claims 1-3, for controlled and continued delivery of melatonin and/or serotonin and/or nicotine and/or mineral salts and/or vitamins and/or antacid substances.
7. A material as defined by the claims 1-3, for controlled and continued delivery of a salt of fluorine (preferably but not exclusively sodium mono-fluoride-phosphate and/or sodium fluoride) and/or calcium and/or magnesium.
8. A material as defined by the claims 1-3, for controlled and continued delivery of sodium hydroxide and/or sodium bicarbonate.
9. Method for controlled and continued delivery of rifaximin from a material adapted to the purpose of holding it in the place of somministration, avoiding its fast and un-controlled dispersion in the neighboring tissues in form of small crystals.
10. Method for controlled and continued delivery of rifaximin without the generation of the unaesthetic an intense red coloration.
11. Method for controlled and continued delivery of rifaximin without the generation of the unaesthetic an intense red coloration, in the oral or pharyngeal or nasal cavity, in the rectum and in the vagina, and from the surface of catheters.
12. Method for controlled and continued delivery of rifaximin by means of a material as defined by claims 1-3.

13. Method for controlled and continued delivery of rifaximin, as defined by claims 9-12, by means of a bi-phasic material, elastic and able to absorb fluid in its pores or molecular interstices.
14. Method for controlled and continued delivery of rifaximin, as defined by claims 9-13, the bi-phasic material, being of benefit for teeth, for the periodontal tissue, for the gum and for the others tissues and organs of the oral cavity.
15. Method for controlled and continued delivery of rifaximin, as defined by claims 9-14, the rifaximin being delivered together with other anti-inflammatory and/or cortisone-based drugs and/or antibiotics and/or antiseptic and/or pain-relief and/or anesthetics and/or anticoagulants.
16. Method for controlled and continued delivery of rifaximin, as defined by claims 9-15, the rifaximin being in association with other antibiotics such as amoxicillin and/or streptomycin and/or penicillin.
17. Method for controlled and continued delivery of rifaximin, as defined by claims 9-14, rifaximin being in association with an anti-viral drug, preferably but not exclusively, such as Ribavirin.
18. Method for controlled and continued delivery of rifaximin, as defined by claims 9-14, rifaximin being delivered in association with other drugs or substances such as nimesulide and/or the acetylsalicylic acid and/or clorexidina.
19. Method for controlled and continued delivery of rifaximin, as defined by claims 9-18, characterized by the fact that rifaximin is deposited on the external or internal surface of a catheter.
20. Method for controlled and continued delivery of rifaximin, as defined by claims 9-18, characterized by the fact that rifaximin is associated to a medical device.
21. Method for controlled and continued delivery of rifaximin, as defined by claims 9-18, characterized by the fact that rifaximin is applied to skin and/or to dermis and/or to other tissues or organs.
22. Method for controlled and continued delivery of rifaximin, as defined by claims 9-18, by means of a periodontal pocket.
23. Method for controlled and continued delivery of rifaximin, as defined by claims 11, characterized by the fact that a material is used, preferably but not exclusively in

oval shape or in a shape of a candle, equipped by a string, or by others means, for its recovery at the end of the use.

24. Method for controlled and continued delivery of rifaximin, as defined by one of the claims 9-23, by means of a material as defined in claims 1-8, for veterinary use.

25. A material or drug delivery system, as defined by one of the claims 1-8, characterized by the fact to have among its components at least one of the following materials: hydrophilic polymers, poly-electrolyte polymers, polymers with carboxylic and/or amino groups, acrylic polymers, polymers and co-polymers of jaluronic acid and other polymers like: polysaccharides (xanthan, guar and similar), cellulose-derivatives, cellulose-cellulose, hydroxy-alkyl cellulose, poly-vinyl-sulfonates, polyacrylates, poly-acrylammides and similar, poly-carboxylates of vinyl and hydroxy-propyl-methyl cellulose.

26. A material or drug delivery system, as defined by one of the claims 1-8, characterized by the fact to be obtained, or to be synthesized, through cycles of freezing and thawing, preferably but not exclusively in an interval of temperature comprised between +20°C and -90°C.

27. A material or drug delivery system, as defined by one of the claims 1-8, characterized by the fact to be obtained, or to be synthesized, by means of a process of partial or total, lyophilization, that is: dehydration, partial or total, through freezing and successive lowering of pressure in order to provoke the subliming of the ice to the inside of the prepared solution.

28. A material or drug delivery system, as defined by one of the claims 1-8, characterized by the fact to be obtained, or to be synthesized, by means of a process of partial, or total, dehydration or drying process.

29. A material or drug delivery system, as defined by one of the claims 1-8, characterized by the fact to be obtained, or to be synthesized, by means of chelating induced by means of divalent or multivalent salt or metal ions.

30. A material or drug delivery system, as defined by one of the claims 1-8, characterized by the fact to contain an adhesive polymer such as: silicones polymers, poly-isobutylene, acrylic polymers, poly-oxyethylene, Polycarbophil, Carbopol, hydroxy-propyl-methyl-cellulose, carboxy-methyl-cellulose, hydroxy-

propyl-cellulose, hydroxy-ethyl-cellulose, Guar rubber, alginates; drum-dried waxy maize starch.

31. A material or drug delivery system, as defined by one of the claims 1-8, characterized by the fact to be applied in place by pressing it onto the surface of interest in order to guarantee its stability and the effectiveness of the release of the substances contained in it.

32. A material or drug delivery system, as defined by one of the claims 1-8, characterized by the fact to have an adhesive element on the external surface, protruding beyond it, in order to be applied in place by attaching itself to the neighboring tissue to guarantee the effectiveness of the release of the substances contained in it.

33. A material or drug delivery system, as defined by one of the claims 1-8, characterized by the fact to have a bi-adhesive element (adhesive from both the faces) in order to be applied in place by attaching itself to the neighboring tissue to guarantee the effectiveness of the release of the substances contained in it.

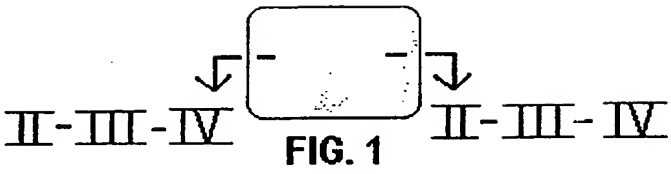

FIG. 1

FIG.2

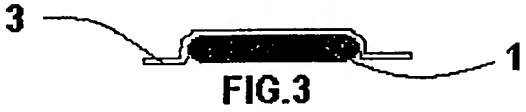

FIG.3

FIG.4